method of administering adrenalin chlorid for prompt relief of certain allergic conditions. They found that a 1:100 solution was frequently effective in the relief of bronchial paroxysm. In August, 1935, adrenalin chlorid solution 1:100 was first supplied to the medical profession to be used in the mouth only, for inhalation by means of a glass nebulizer.

It occurred to us that this same adrenalin chlorid preparation could be used as drops in the conjunctival sac; and since December, 1935, we have thus employed it in over one hundred cases with most satisfactory results.

We have found it to be a very effective therapeutic agent in iritis and in glaucoma secondary to uveitis. In has been our impression that exudation was markedly relieved by constriction of the vessels of the iris, and that as a result of this the formation of pupillary membranes, posterior adhesions and blocking of the filtration angle by exudate, with consequent secondary glaucoma, were prevented and relieved.

In our experience adrenalin 1:100 substitutes well for, and from many points of view is preferable to, the present and past methods of applying suprarenin products in ophthalmology, such as by subconjunctival injections[3] or the placing of wicks[4] of cotton saturated with a solution of adrenalin chlorid 1:1000, or by the use of concentrated solutions of synthetic epinephrin products, glaucosan[5] and suprarenin bitartrate.[6] Its further uses and advantages will be reported at a later date in the ophthalmologic journals.

490 Post Street.

OTTO BARKAN
S. MAISLER
San Francisco.

[3] Erdmann: Subconjunctival Injections of Suprarenin Preparations, Klin Monatsbl. f. Augenh., 52:520, 1913.

[4] Gradle, H. S.: The Use of Epinephrin in Ocular Hypertension, J. A. M. A., 84:675 (Feb. 28), 1925.

[5] Hamburger, C.: Ersatzpräparate für Adrenalin und ihre Bedeutung für die Glaukombehandlung, Med. Klin., Vol. 21, Part 2, pp. 1495-1498, 1925.

[6] Funk, C., Dubin, H. E., and Freedman, L.: J. Am. Pharm. A., 12:952, 1923.

Syphilis Is Preventable.—Syphilis is a disease of civilization and flourishes particularly in communities where there is a massing of individuals. Under such conditions, the opportunities for its spread are very much greater. It depends more upon faulty social conditions than almost any other communicable disease. While prostitution is a tremendous factor in spreading the infection, a very large number of cases are contracted outside of prostitution. It causes more mental and physical suffering than any other known disease. It is preventable and at the present time may be considered as curable. Yet it is doubtful that any other disease can compare with it in the intensity and severity of its onslaughts. Its control is greatly hampered by the attitude of the general public which too often attaches a social stigma to it. Syphilis should be regarded the same as any other infectious disease. The mere fact that it is often venereal in its origin should not hamper its control. Gradually, however, the old idea that it is punishment for sin has become dispelled. Fortunately, a new trend of public opinion can be observed. This has to do with enlightenment, the spreading of knowledge relative to the cause, effects, prevention, and treatment, all of which must be closely bound together in any program for the control of the disease.

ORIGINAL ARTICLES

CLINICAL PATHOLOGICAL CONFERENCE*

PROCEEDINGS: CORONADO ANNUAL SESSION

Foreword by President Robert A. Peers.—This morning you will notice, from the announcements which have been handed you, that we are departing from the ordinary type of program, and I think it is going to prove excellent. We have with us as an invited guest a man whom many of you know personally, and most of you know by reputation. He is Professor of Medicine at McGill University in Montreal, formerly assistant resident physician at Hopkins under the late Sir William Osler, and also later a Professor of Medicine at the University of Iowa. I feel particularly happy in introducing this speaker because, as perhaps many of you know, I am an ex-Canadian myself. It is a great pleasure to present to you this man from my former homeland, a member of a great race, a representative of a great friendly neighboring country, and a colleague from a great medical school. Ladies and gentlemen, Dr. Campbell P. Howard, Professor of Medicine at McGill University, Montreal, who will take charge of the Clinical-Pathological Conference on this morning's program. Doctor Howard.

REMARKS BY DR. CAMPBELL P. HOWARD

DOCTOR HOWARD: Doctor Peers, I hardly need to say how much I appreciate your kind reference to our sympathy in our homeland. When your Program Committee decided on this adventure, and thought of the Clinical-Pathological Conference, they had to look around for the best-natured clinician available, and someone on the committee knew that I was speaking on the day before and said, "Probably that old fellow, Howard, won't mind holding it." You have to be good-natured to hold a clinical-pathological conference, because what little pride has been left you by previous mistakes is lost at the first autopsy, as you will see presently. I have grown so accustomed to it that I no longer mind and really get as much "kick" as a pathologist does at being wrong. The only thing that I still feel it is my duty to do is to do my best, and after taking or reading a carefully prepared history, both family and personal, and of present illness, having made a complete physical examination, applied all the simple laboratory tests, and called upon my assistants in some of the more elaborate ones, I feel that I am entitled to say that I have done the best that I can. Adding up, then, the results, I feel permitted, as a rule, to come to some pretty definite conclusions. I was taught that it is my duty, or your duty, having done all those things, not to have the point of view that the case should be explored by a friendly or unfriendly surgeon, or a diagnosis made by a friendly or unfriendly pathologist. I do not think

* The Clinical Pathological Conference was held on Tuesday morning, May 26, 1936, at the sixty-fifth annual session of the California Medical Association, May 25 to 28, 1936.

Led by the late Campbell P. Howard, M. D., whose death occurred in Santa Monica, California, on June 3, 1936. (CALIFORNIA AND WESTERN MEDICINE, July, 1936, pages 4 and 102.)

that we are doing our part if we do not make the very best attempt at making a clinical diagnosis, and we insist that our students, interns, and staff write down a diagnosis as soon as the case has been partially studied. First-sight impressions, final clinical diagnosis—and then along comes the pathologist, and very often we disagree. This committee that was appointed to assist me, comprising eight men, pathologically inclined, have asked me to deal kindly with them. I am going to ask them to deal kindly with me. They have chosen very good cases and submitted six for our selection. I picked four of those six. They have drawn up in these little folders an outline, which I am going to read to you, of the case, and, at the end, the autopsy findings. I would ask you not to read the autopsy findings. Had we had time yesterday we would have obliterated from this public list the autopsy findings, so let us play cricket and not look at them. They will be a surprise to us and we will enjoy them much more if we have the surprise later.

CASE I

This first patient (history will be presented pathologically by Doctor Hall), was a white laborer, fifty-five years of age, who entered a hospital on July 25, 1935, complaining of attacks characterized by sudden loss of consciousness; pain in precordial region; shortness of breath on mild exertion; swelling of the feet and ankles. Well, one does not need to be a Sherlock Holmes with those presenting symptoms to have an impression, and I think we are justified in saying right here that that sounds undoubtedly like a cardiovascular syndrome, and our attack in the history taking should be to lay special stress on the family and personal history of cardiovascular disease. I think we are perfectly wise in admitting that.

The family history is uneventful. His own personal history, not taking that in quite the order submitted, is important, because he has been a heavy worker all his life, a day-laborer, earning his bread by the sweat of his brow. He has used alcohol and tobacco very moderately. I do not believe that is of either negative or positive importance. Being a user of both in moderation, I do not think they play very much of a rôle in the etiology of most diseases. More important than that, certainly, is a story of one severe previous illness which was diagnosed as blood poisoning; we will call it septicemia of some sort. It followed an injury to his leg. It may have been septical pyemia. That occurred in 1917, and may have left its mark on the cardiovascular tree, as we know, myocardial, possibly endocardial, and certainly arterial. The pneumonia for two months in 1922 is hardly a significant note. There is no history of a primary sore. The gonorrhea of 1925 is too distant to be significant.

Nine months before entry to the hospital, he noticed moderate loss of strength and endurance, a mild degree of nausea, and lack of his usual feeling of good health. He was given treatment and his condition improved, and he returned to work as a laborer. Three months ago he noticed shortness of breath on exertion, swelling of the feet and ankles, and felt unable to continue work. At this time, while at home, he suddenly became dizzy, lost consciousness, and was unconscious for a period of about forty-five minutes. He rested at home, was fairly comfortable, but continued to have shortness of breath on exertion. Three days and one day before entry he had attacks of unconsciousness lasting about a half-hour, followed by severe pain in the precordium, the neck and the left arm, and profuse perspiration, with cold, clammy skin. On entry he complained of these pains; severe headache and stiffness of the legs.

These attacks of loss of consciousness naturally arrest one's attention for a moment. He had three such attacks. What, in a cardiovascular history such as this, do they signify? Naturally, some cerebral accident, and from experience of my own I think I could say small hemorrhages, perivascular hemorrhages, following a spasm of one of the cerebral arteries, associated with the diapedesis of red cells, giving an injury which lasted but a short time. These later attacks, associated with Traunley's syndrome, are still more significant, and suggest another angiospasm in another region, coronary. So that cerebral angiospasm, coronary angiospasm, with interference with function of the brain and with further interference with function of the heart, are important points in that history. If I had to make a diagnosis at this stage, I would say that in a laborer of fifty-five we are dealing with arteriosclerotic heart disease, cerebral arteriosclerosis, coronary arteriosclerosis, but he might be a hypertensive. He is on the borderline, as far as age is concerned; but he is a laborer and we see more cases of arteriosclerotic heart disease among the laborers than we do of hypertensive cardiovascular.

Doctor Hall reports that, at physical examination, the patient's temperature was normal; his pulse was only 72, his respirations were 20, and he weighed 170 pounds. The blood pressure, on admission, was recorded as 160/110. General routine physical examination revealed a strongly built man, large frame, and powerful muscles. Poor dental hygiene. The heart was enlarged to the left, and there was a moderately loud systolic murmur at the apex. Pigmented scars over the anterior tibial surfaces—a laborer—so he was entitled to them. The reflexes were normal. The urine was negative, except for an occasional hyaline cast. There were no blood cells. The blood count was, to all intents and purposes, normal. Hemoglobin was 80 per cent, 4,500,000 reds, with normal leukocytes. His blood Wassermann was negative, so syphilitic heart disease, I should say hypertensive heart disease, is ruled out. My pathological friends may not agree, but I am not looking at the anatomical diagnosis now; I have forgotten it.

The electrocardiogram indicated coronary disease, and subsequent records taken during the next ten days confirmed this interpretation.

During the first five days in the hospital he complained of much pain in the precordium, neck, and both arms, but more severe in the left. Narcotics relieved the pain. Blood pressure rose to

180/70 (your printed report states it fell, which is evidently an error), and temperature remained normal. He continued to have occasional attacks of pain, but his condition improved gradually. Electrocardiogram tracings still presented evidence of coronary thrombosis.

I cannot accept that. I have never seen a case of coronary thrombosis with a blood pressure, whether it had risen or fallen, of 180/70. Everything is possible, of course, in medicine, but speaking from experience—for one has to speak from experience—that is not evidence of coronary thrombosis. I do not care what the electrocardiogram will show. I am old-fashioned enough, too well trained by Osler, to accept any laboratory dictum. I should not get annoyed about it, but if I am going to get annoyed about anything it is that—to have some smart alec come in and tell me that man has coronary thrombosis. I call it vigilance. (Laughter.) Mind you, I want electrocardiograms; I ask for as many electrocardiograms as anybody does, and I want the expert to say what he thinks; but that report goes into the positive column only through the negative column, just as the positive Wassermann or the negative Wassermann, the albumin urine, or what not. It is not a positive finding like tubercle bacilli in the sputum or typhoid bacilli in the blood, etc. It is a clinical finding of great importance, but I do not believe, and I ask you to think about it in the future, that it should be taken too seriously. Now, the electrocardiogram reported coronary thrombosis. The man had no fever, one of the symptoms of it. The leukocytes are not given at any particular time, but we are told that at one time they were 8,200. He had no leukocytosis. His blood pressure remained at a level of 180/70. No pericardial friction rub was heard. We do not expect that in more than 25 or 30 per cent of the cases. But that does not sound to me like coronary thrombosis. It sounds to me like hardening of the arteries disease, with angina and possibly a persistent angina, almost the status anginosis of Clifford Orbutt. These are the remarks I have to make about the case at this stage.

When he had been in the hospital about nine weeks, more interesting things developed. First, a low-grade fever, fluctuating between 99 and 101 degrees, and the pulse rate rose to 100. You recall his admission pulse rate was 72. The precordial pain had practically disappeared; of course, that would happen even in coronary thrombosis by this time. He developed, however, transient redness, swelling, pain, and tenderness in various joints of the extremities. I would like you to remember that, because I am going to refer to it in a moment. He developed an arthritis, or an arthralgia. His appetite became poor, he lost weight, his temperature became higher, a leukocytosis developed (18,000), the hemoglobin dropped to 60 per cent, and a blood culture on October 28 revealed Streptococcus viridans. And now we know that the patient has a septicemia due to the Streptococcus viridans, the organism so quickly associated with subacute bacterial endocarditis. Looking back to that development of fever, malaise, loss of weight, and leukocytosis, plus the arthralgic symptoms, I could say at this point, if the case were mine, that this man has developed on top of an arteriosclerotic heart a subacute bacterial endocarditis, and his days are numbered. Blood and albumin appeared in the urine, whereas on admission they had been negative. Profuse perspiration, great loss of weight, and weakness developed. Acute pain, note, in the left upper quadrant of the abdomen, later in the right lower quadrant. Blood and albumin were found in the urine. With these episodes, which were of two to five days' duration, there was marked tenderness, but practically no increased rigidity over the abdominal wall in the region of the spleen or elsewhere. The systolic murmur at the apex did not change. During December, petechiae developed, not only in the skin but in the mucous membranes of the mouth and in the conjunctivae. We have the whole picture of subacute bacterial endocarditis, as first called to our attention by Manuel Lipman of Mount Sinai Hospital many years ago, and now a well-recognized clinical condition, just as well recognized as typhoid fever or tuberculosis.

He became semicomatose, developed signs of pneumonia, and died January 20, 1936, greatly emaciated, very anemic, and exhausted.

The diagnosis on entry, the report states, was hypertension, cardiac hypertrophy, and coronary thrombosis. Hypertension at 160? No! I disagree. That is not essential hypertension. That is the hypertension secondary to arteriosclerosis. Cardiac hypertrophy, yes; coronary thrombosis, no.

Then the final diagnosis of subacute bacterial endocarditis was made. It had been suggested that, since the heart murmur was only an apical systolic murmur and did not change throughout the course of the disease, there may have developed a mural thrombus in the heart which resulted from the coronary thrombosis which was suspected; a very plausible explanation—a very nice explanation. I agree with that, and say it was very smart, a good idea with the diagnosis of coronary thrombosis.

The terminal bronchopneumonia, the infarcts of the spleen and kidneys are of no great interest. The terminal bronchopneumonia is a terminal event in every acutely febrile case, and the infarction of the spleen and kidney is part and parcel to subacute bacterial endocarditis.

Now, ladies and gentlemen, we will hear what our friends, the pathologists, have to say, and I know that you do not need to tell them not to spare me or my blushes.

Report of the Pathologists:

DOCTOR HALL: Doctor Peers, Doctor Howard, Members of the Society: I am sure we shall not let Doctor Howard down very severely in this case.

. . . Doctor Hall reads autopsy report. . . .

COMMENT

DOCTOR HOWARD: I think you will agree we got off rather easily that time. I feel that the explanation for every symptom was there. Every

clinical laboratory finding was there in the autopsy, and the only thing that we have to criticize is the stress that was given to the report of coronary thrombosis by the electrocardiogram. The patient also should not have been considered a hypertensive. We will say more about that in the next case. It is too easily applied. A nurse can be trained to take a blood pressure, and if it is just a question of taking a blood pressure and calling a patient hypertensive, we should go out of business; certainly not spend four to eight years in training. I would suggest to you: never be satisfied with the diagnosis of hypertension and only after mature consideration, weighing the pros and cons, make a diagnosis of essential hypertension. So many other conditions may give rise to an increase in blood pressure of a moderate degree.

* * *

CASE 2

The second case is one that is much more unusual and very instructive.

The patient was a woman whose pathological findings Doctor Maner will discuss. Forty years of age, married seventeen years, and observed at the hospital from March 10 to March 17, 1934. Second admission, March 31 to April 1, 1934. She finally died at home on May 11, 1934.

The family history is negative.

The past history reveals a lot of infections. Scarlet fever is the most important one notoriously in relation to the kidney, and possibly some of you would overstress that from the subsequent developments. Some of you would say that this woman of forty at the age of three had acquired a glomerular nephritis which was eventually responsible for her terminal symptoms. Then so-called "typhoid malaria" at the age of eight; I place it in quotation marks because there is no such animal, as we all know. She had some infection at the age of eight, presumably typhoid. She also had, following this, measles in moderate severity, and then symptoms of frequency of urination, nocturia, and slight edema for several years. She was a multipara, had three children, all in good health. She had three abortions.

The present illness began two years before coming under observation, with a stroke, causing partial paralysis of the left side of the face, the left arm, and the leg. After a few months she recovered and has since noticed only a slight weakness on that side. The diagnosis at that time was hypertension and nephritis. I have nothing to say to that. Also, of course, we could assume that she had a leak into her vein from an artery, resulting in that partial paralysis of the left side of the body. The systolic blood pressure at that time, two years ago, was only 200. Not marked; it was high. There was some polyuria as also nocturia.

About January 26, 1934, a second stroke occurred, involving this time the right side. She was taken to a hospital, where she remained about two weeks. During that time she had such severe headaches, nausea, and vomiting, that a spinal puncture was done to relieve the intracranial pressure. A little later an osteopathic physician was consulted, and he was a good salesman and told the patient that she was suffering from a syphilitic brain tumor about the size of a walnut (it does not say with the shell on or without—I would like to know) in the posterior portion of the brain, which was pressing on the nerves, causing all her symptoms, *i. e.,* the headache, nausea, vomiting, high blood pressure, nocturia, etc. What is possibly more important is that the spinal fluid Wassermann was three plus.

Now, I would like to stop here. I would have been very much up in the air because here is a woman of forty, with symptoms of cerebral spinal disease and a spinal fluid which was three plus. Of course, it will not explain the hypertension, but one would naturally have to consider cerebrospinal vascular lues.

On March 3, 1934, the patient was brought to the office of another physician for verification of the osteopath's diagnosis. At this time all the symptoms of nausea, vomiting, severe headaches, were more severe, and she was beginning to complain of inability to see clearly, especially in reading. Hospitalization was advised and she entered the hospital again for diagnosis and the relief of her symptoms. At this time she was still fairly well nourished, extremely nervous, apprehensive, no doubt, lying in bed, with no evidence of dyspnea. Temperature was 99 degrees; respiration, 18; pulse, 110, full and bounding; blood pressure, 240/150. I think all agree that a diastolic pressure above 100 is a significant fact, and I think that at this point any one of us would be justified in saying, "Never mind the symptoms for the moment; we are dealing with malignant hypertension, anyway." What do I mean by malignant hypertension? But I know you know much more than two or three of my recent students who, in an examination on malignant hypertension which they were asked to discuss, said, in one case, "I know nothing about it; I have never heard of it." Another said, "I know so little about it, as apparently is true of Lewis, who has devoted only a small paragraph to the subject in his textbook on diseases of the heart." I did not take the trouble to verify that statement. I think it may have been true because Lewis is an electrocardiograph specialist. He is a physiologist and a cardiologist, but he is not a clinician, and he may not think that malignant hypertension is an important question. We in hospitals have to disagree with him. We believe it is a very important question.

Let me remind you that it was many years ago that Gullen Sutton pointed out that the most important thing about any disease was the arterial lesion, and when the sphygmograph was introduced by Bausch in 1893, a clinical instrument of great value was put on the market. The wonderful writings of Clifford Orbutt helped to interest the medical student in the problems of hypertension, and he it was who coined the term "essential hypertension." His two volumes on "Arteriosclerosis and Diseases of the Artery" are still classics. Thanks are due to Bolard and Farre, who pointed out that there was a group of cases which

might be termed truly malignant, and that the majority of cases of essential hypertension were benign. So that we began to think in 1914 of the benign and the malignant nephrosclerosis, those at least who had read Bolard and Farre's monograph. Later Farre suggested that the term "malignant" should be applied most emphatically to this group, and he would add the term "malignant nephrosclerosis," not merely malignant hypertension. His pathologic studies had so impressed him with the fact that the main suffering organ was the kidney that he said, "We will not speak of malignant hypertension alone. We will say malignant nephrosclerosis." Then, later in this country and elsewhere, Keith and Wagoner, studying a large group of cases, stressed even more so this lesion in the kidney described by Bolard and Farre, and even suggested that it is a distinct entity, that it is as much an entity as chronic glomerular nephritis, and that malignant hypertension does not develop merely as a result of essential hypertension of the benign type, but is malignant from the beginning of things. While I am not prepared to agree with that, I want to say that in looking over this history and the clinical findings to date, I would be inclined to regard this case now as malignant nephrosclerosis.

The examination of the patient was otherwise unimportant. The laboratory findings revealed a urine containing two plus albumin, rare hyaline cast, two to three red cells per high power field, and some leukocytes in this centrifugalized sediment. Other urine samples showed a specific gravity ranging from 1.015 to 1.017, an almost fixed specific gravity; no hematuria; no further casts found. So that we have evidence, then, of the malignant sclerotic disease. The blood count showed a slight reduction of the reds and the hemoglobin, a slight leukocytosis, and Wassermann tests were negative, as were Kahn tests. The spinal fluid showed marked increase in pressure, but only three cells. No increase in globulin. The next Wassermann was negative. The report does not say who took that spinal fluid that was sent before. I presume it was done in the hospital and, as often happens, the Wassermann is a false positive. Certainly, the examination subsequently of the spinal fluid rules out cerebrospinal vascular syphilis. The concentration test of the urine showed fixed specific gravity. A contracted kidney followed this. The blood chemistry showed retention of a moderate degree of nonprotein nitrogen. Uremia was impending. The treatment was the classical one of glucose intravenously daily, luminal sedatives, magnesium sulphate, and pancreatic tissue extract. I have never had any experience with that, so I cannot criticize.

The progress of the case was downward. The pulse ranged from 80 to 100; the blood pressure reached 256/190—it never fell below 172/130, and that was after intravenous glucose saline. Nausea and vomiting stopped. During the first few days, the patient was incoherent in speech and disoriented at times and very restless, as these patients nearly always are—apprehensive and restless as can be.

After a week she was allowed to go home. All nausea and vomiting ceased. Two weeks later she reported for another spinal puncture, with relief. The spinal fluid was not under the former high pressure, but the patient experienced marked relief from her headaches, etc.

From April to May 10 she was at home in bed, attended by a private nurse. During that interval she gradually became weaker, had a return of vomiting, and lost the sight of both eyes. No doubt, had a fundus examination been made at this time there would have been an extensive hemorrhagic uroretinitis, which in itself has its peculiar features and is so well recognized that our ophthalmologist often has the temerity to report malignant hypertension, nephrosclerosis, before we have made the diagnosis. Once he hurt our feelings very much in this, but we proved later to be right.

The patient finally died, so the diagnosis seems, to one who knows malignant nephrosclerosis of Bolard and Farre, to be a straight case of malignant nephrosclerosis. There is nothing more to say about it. The course of a few months is the usual one. The disease rarely lasts more than a year. It is to be separated entirely from secondary contracted kidney and from nephritis. It gives many symptoms that simulate the secondary contracted kidney, and very often one finds the condition adhering to that diagnosis in spite of the description of the other condition which I have just given you. We want you to bear that in mind—that there is such a disease as malignant hypertension, usually occurring in women and younger men, running a rapidly progressive course and ending in uremia, rapidly developed in the majority of cases, cardiac failure, or cerebral accident.

Now we are going to hear what the pathologic findings were. Doctor Maner.

Report of the Pathologist:

DOCTOR MANER: I may add that the Wassermann in this particular case that the doctor mentions was done by the osteopath. The necropsy here was performed by Doctor Foord, and was studied and presented by me through his courtesy.

. . . Doctor Maner reads his report. . . .

* * *

CASE 3

DOCTOR HOWARD: Doctor Budd will report on the third case which we selected. This was a young married woman of thirty-four, who had nothing of really great importance in her past medical history; measles, mumps, pertussis, chicken pox, etc. Her tonsils and adenoids were removed in 1921 for frequent sore throat. A severe bronchitis or bronchopneumonia occurred in 1932, from which the patient slowly recovered. There has been an intermittent fever with chills for the past eight years, and a diagnosis of malaria was made at one time. I am going to ask Doctor Budd afterward where she lived, and whether it was possible that she did have malaria at that time. Naturally, anybody remembering the Pel Epstein syndrome occurring in the later stages of Hodgkin's disease,

might think that that malaria-like fever could have been a Pel Epstein syndrome. I have known a case of Hodgkin's disease to last as long as that with a history of Pel Epstein syndrome eight years before, so I am more inclined to think that that intermittent fever with chills was probably a malaria, although it would depend upon the place of residence both in childhood and adolescence. She has had attacks of severe headache intermittently all her life, causing vomiting—migraine, in all probability—and of no interest. The patient has been very emotional, and her hair turned gray prematurely six years ago, at the age of twenty-eight. That is not an uncommon associated phenomenon in my experience with migraine. The family history is irrelevant. She complained, when she was admitted, of enlargement of the spleen, enlargement of the glands, loss of strength, loss of weight and appetite, and jaundice.

The illness dated back to April, 1934, when she first developed a painful lump in the left upper neck. There was a memory of a mild sore throat prior to this. The virus of Hodgkin's disease is usually supposed to enter through the nasal passages. Her general condition remained good until September of the same year, when three enlarged lymph glands were discovered in the left cervical chain. These glands were symptomless, and in February, 1935, one of them was removed for biopsy. The diagnosis reported by the pathologist was Hodgkin's disease. The patient remained in good health and continued to work, although she had a mild anemia and intermittent fever up to 101 degrees.

During March, 1935, high voltage x-ray therapy was given to the enlarged glands in the left neck, mediastinum, and upper peritoneal cavity and to the enlarged spleen. A prompt regression of glands occurred, with improvement in health and a gain of fifteen pounds in weight.

The blood count at this time, we are told, showed slight anemia, 80 per cent hemoglobin, with a leukopenia of 4,300, but that leukopenia was peculiar because, contrary to most leukopenias, the polymorphonuclears were relatively increased—79 per cent. Small lymphocytes were only 11; large lymphocytes, 1; transitional cells, possibly the only significant thing in the differential, 5; eosinophils, 3; and basophils, 1. The picture is one that is quite in keeping with Hodgkin's disease. Its negative Wassermann exists habitually, and the most peculiar thing was the leukopenia with polymorphonuclears in regard to this.

The patient remained well until August, 1935, at which time examination revealed the eyes, nose, and throat to be normal; teeth sound; and chest, heart, and lungs normal. Two indurated glands were found in the right axilla and one in the left axilla. There was an abnormal resistance in the epigastrium from an obvious retroperitoneal mass of undetermined size. The liver and spleen could not be felt. Shotty glands were present in both groins of only suspicious character.

Radiographic studies of the ribs, lungs, and mediastinum failed to reveal any evidence of abnormal pathology.

The blood count then revealed a hemoglobin of 64 per cent, a drop; reds of 4,290,000; whites of 4,900; and no malaria parasites could be found. She had a further x-ray treatment.

The patient remained in good health until the first part of December, when she began to suffer with severe headaches, a fever of 101 degrees, and greatly increased jaundice. That, of course, is an unusual feature, and at once attracts one's attention. I feel certain that we would suspect, as sometimes occurs in so-called abdominal Hodgkin's disease, involvement of a group of glands somewhere near the common duct and pressing on the common duct, and resulting in an obstructive jaundice. Loss of appetite and strength and weight persisted.

The blood count on January 6 showed a further drop, 22 per cent; reds, 1,410,000; and the whites were still lower, 1,500. Differential count showed that same polymorphonuclears predominance, 95, of which 3 were juvenile, 20 stab, and 72 were the ordinary segmented forms; monocytes, 3; plasma cells, 1; and myelocytes, 1. The red cells were of varying size and shape. The average size of the cell was approximately normal. There was a moderate poikilocytosis. There was some polychromatophilia. There was a complete absence of lymphocytes, with a marked left shift in the polymorphonuclears. The platelets were now distinctly reduced in number. Of course, she had had so much x-ray therapy one might very well expect that. My only regret is, from what I have read about the case, that we do not know what the platelets were when she first came under observation. As many of you know, Buerke of Madison, Wisconsin, many years ago, when he was still an assistant in pathology to Welch and Hopkins, found and stressed the frequency of an increased platelet count as a feature of Hodgkin's disease; and we have accepted that at its face value. We do not rule out Hodgkin's when it is not present, but it is very, very frequently present. If I were to have a blood report on the case, as I naturally would like in every case, I would rather have the platelet than anything else. There is nearly always in the early stage, before x-ray therapy or radium therapy has been instituted, an increase in the platelets. The urine was reported as negative except for the urobilin much increased, urobilinogen also increased, and the stool examination was negative.

The patient was finally hospitalized with the hope of controlling the nausea. The blood counts revealed further anemia. The direct Van den Bergh showed an immediate heavy positive; indirect Van den Bergh, 16 units. She was given blood transfusions at weekly intervals without apparent benefit. The stool examination remained normal. On January 25 the blood count was still further reduced: 19 per cent hemoglobin, 880,000 reds, white blood cells 1,400; and there were 9 lymphocytes now. The jaundice was extreme and the patient was irrational. There was marked edema of all the tissues, and the liver and spleen now both reached two fingerbreadths below the costal margin. She died on January 26, 1936.

Of course we had the biopsy, which we should have in every case. If you ever miss Hodgkin's disease it is your own fault, because early in the disease a biopsy should be done. Now to confess the truth, in spite of my knowledge of that, I missed a case of Hodgkin's disease in a young Irish-Canadian woman who was the picture of tuberculosis: the dark swarthy type, with hair on her forearms and legs, emaciated, having glands in the neck, a cough, a mediastinal dullness, and an x-ray plate which showed plainly the mottling of the lung and calcified areas of the tracheobronchial type of an early childhood tuberculosis. The clinician told me that she had a positive Von Pirquet of one to ten thousand. She had a little fever, she was sweating, and she had all the symptoms of tuberculosis of the lungs. She was coughing, but no tubercle bacilli could be found. We advised sanitarium treatment, but she did very badly under it. She was sent home by the sanitarium physician, a wise man, saying that this was not tuberculosis; it was Hodgkin's. When she came home we had, then, to my shame, what I should have ordered before, a biopsy, and it was Hodgkin's. She is dying now from Hodgkin's. So, in any suspicious case, as this case well illustrates, a biopsy will make the diagnosis because —as Dorothy Reed McCallum pointed out long ago; Sternberg, too, of course—there is a histologic picture in the glands that occurs in no other condition, whether or not you accept the Dorothy Reed specificity or the Dorothy Reed cell. Whether you accept it or not, there is a combined histologic picture which I think cannot be questioned, and the histologists in this country are perfectly ready to accept it and to make a diagnosis for you early, as early as the gland is submitted. Doctor Foord is going to discuss this case.

Report of the Pathologist:

DOCTOR FOORD: Mr. Chairman, Gentlemen: The interesting thing to me was the profound anemia which came on six months after x-ray was stopped, and in our postmortem I think we can explain some of the causes.

. . . Doctor Foord reads his report.

COMMENT

DOCTOR HOWARD: Now, ladies and gentlemen, we got a surprise there in the finding in the bone marrow. It is, I am sure, clinically a very rare event and also pathologically, as far as my case could go. I recall only one similar case in which the bone marrow was so extensively involved, so our interpretation of the absence of platelets and the low blood count of progressive anemia as due to possible over-x-ray radiation was not justified, and Doctor Foord has given you the explanation in the destruction of the hematopoietic system by invasion of Hodgkin's tissue.

IN CONCLUSION

You have been very kind and considerate, but my time is up and I am going to ask the privilege of calling it a day's work. Doctor Budd had a very interesting case of acute lymphatic leukemia for us, but as it is half-past twelve and I know you are tired we are going to close the discussion. (Applause.)

* * *

PRESIDENT PEERS: One moment, please. I think your chairman should express his great pleasure at the success of this conference. I think that this innovation, which has been introduced by the Program Committee, has been a wonderful success and it has been due to a number of factors. First, we have had a number of men who have given a great deal of time to the preparation of this program and worked the cases up well and had autopsy reports. Then, in addition to that—and here is a suggestion for any future programs of this sort—we hope that you can get a leader with the great experience and the wide knowledge and keen analytical mind of the gentleman who presided this morning at this conference. If you could get one with the same kindly humor and charming manner of delivery as our friend here, I am sure that the next conference of this sort will be a great success. I thank you, Doctor Howard, and I thank all the members of and leaders in this conference for the splendid work they have done in making such a wonderful success of the morning. Thank you very much. (Applause.)

. . . The meeting was adjourned by President Peers.

PROTAMIN INSULIN: SOME CLINICAL STUDIES

CALCIUM AND ZINC PREPARATIONS WITH INSULIN

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THE studies comprising this report are a continuation of those previously reported on the use of simple protamin insulin,[1] and are concerned with mixtures of calcium and zinc in the precipitated insulin, including the present zinc series of the more stable mixed form.* A total of 174 patients have been under observation with protamin insulin therapy, and 150 are included in this report. Of these, eighty-eight patients are adults and sixty-two are juveniles, with an age range from 18 months to 79 years. Forty-five patients have been hospitalized for a closer study at the beginning of protamin treatment. Daily urine analyses were made on these patients. Ambulatory patients have been seen once a week, with analyses of urine on each visit. Urines have been routinely collected in two twelve-hour periods to cover the full twenty-four hours immediately before the visit, and the daily analyses for all hospitalized patients have been collected in the same two

* All preparations of protamin insulin used in these studies have been supplied by the Eli Lilly Company, and appreciation is now expressed for the courtesy and generosity this company has shown throughout the work.

All clinic patients selected for this study are from the diabetic services of the Cedars of Lebanon and Children's hospitals. The interest and coöperation shown by the various staffs of these institutions have been of great help.